FILE CAPLUS 4/12/07

10/522,646

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L5 ANSWER 1 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:394676 CAPLUS
TITLE: Determination of Fenofibric Acid Concentrations by HPLC After Anion Exchange Solid-Phase Extraction From Human Serum
AUTHOR(S): Straka, Robert J.; Burkhardt, R. Todd; Fisher, James E.
CORPORATE SOURCE: University of Minnesota College of Pharmacy, ., Department of Experimental and Clinical Pharmacology, Minneapolis, MN, USA
SOURCE: Therapeutic Drug Monitoring (2007), 29(2), 197-202
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Triglycerides are increasingly being recognized as a risk factor for cardiovascular disease. Research efforts to identify sources of variability in triglyceride-lowering response to the lipid-lowering drug fenofibrate require quantification of the active acidic form of this PPAR-α agonist. Anion-exchange solid-phase extraction, in combination with reverse-phase high-performance liquid chromatog. (HPLC), rapidly and accurately dets. steady-state fenofibric acid serum concns. Chromatog. separation under isocratic conditions, with use of UV detection at 285 nm, provides clean baseline and sharp peaks for clofibric acid, 1-naphthyl acetic acid (internal stds.), and fenofibric acid. Commonly prescribed and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) were screened for assay interference, and the assay was employed to quantify fenofibric acid in more than 800 human subject specimens. Fenofibric acid anal. was found to be linear over the range of 0.5 to 40 mg/L and was validated with either internal standard Accuracies ranged from 98.65% to 102.4%, whereas the within- and between-day precisions ranged from 1.0% to 2.2% and 2.0% to 6.2%, resp. NSAIDs had minimal interference with the assay, which succeeded in quantifying fenofibric acid in more than 843 of 846 serum samples from human subjects, many taking a variety of coadministered medications. Anion-exchange solid-phase extraction in combination with reverse-phase HPLC accurately dets. steady-state fenofibric acid serum concns. in humans without interference from NSAIDs or commonly administered medications. This method is suitable for quantification of fenofibric acid for clin. pharmacokinetic studies in patients with dyslipidemia.

L5 ANSWER 2 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:363075 CAPLUS
DOCUMENT NUMBER: 146:309025
TITLE: Effects of a potent and selective PPAR-. alpha. agonist in patients with atherogenic dyslipidemia or hypercholesterolemia. Two randomized controlled trials
AUTHOR(S): Nissen, Steven E.; Nicholls, Stephen J.; Wolski, Kathy; Howey, Daniel C.; McErlean, Ellen; Wang, Ming-Dauh; Gomez, Elisa V.; Russo, John M.
CORPORATE SOURCE: Department of Cardiovascular Medicine, Cleveland Clinic Lerner School of Medicine, Cleveland, OH, USA
SOURCE: JAMA, the Journal of the American Medical Association (2007), 297(12), 1362-1373
CODEN: JAMAAP; ISSN: 0098-7484
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LSN862 is a novel peroxisome proliferator-activated receptor (PPAR)α/γ dual agonist with a unique in vitro profile that shows improvements on glucose and lipid levels in rodent models of type 2 diabetes and dyslipidemia. Data from in vitro binding, cotransfection, and cofactor recruitment assays characterize LSN862 as a high-affinity PPARγ partial agonist with relatively less but significant PPARα agonist activity.
Using these same assays, rosiglitazone was characterized as a high-affinity PPARγ full agonist with no PPARα activity. When administered to Zucker diabetic fatty rats, LSN862 displayed significant glucose and triglyceride lowering and a significantly greater increase in adiponectin levels compared with rosiglitazone. Expression of genes involved in metabolic pathways in the liver and in two fat depots from compound treated Zucker diabetic fatty rats was evaluated. Only LSN862 significantly elevated mRNA levels of pyruvate dehydrogenase kinase isoenzyme 4 and bifunctional enzyme in the liver and lipoprotein lipase in both fat depots. In contrast, both LSN862 and rosiglitazone decreased phosphoenol pyruvate carboxykinase in the liver and increased malic enzyme mRNA levels in the fat. In addition, LSN862 was examined in a second rodent model of type 2 diabetes, db/db mice. In this study, LSN862 demonstrated statistically better antidiabetic efficacy compared with rosiglitazone with an equivalent side effect profile. LSN862, rosiglitazone, and fenofibrate were each evaluated in the humanized apoA1 transgenic mouse. At the highest dose administered, LSN862 and fenofibrate reduced very low-d. lipoprotein cholesterol, whereas, rosiglitazone increased very low-d. lipoprotein cholesterol. LSN862, fenofibrate, and rosiglitazone produced maximal increases in high-d. lipoprotein cholesterol of 65, 54, and 30%, resp. These findings show that PPARγ full agonist activity is not necessary to achieve potent and efficacious insulin-sensitizing benefits and demonstrate the therapeutic advantages of a PPARα/γ dual agonist.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 52 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:463191 CAPLUS
DOCUMENT NUMBER: 143:186489
TITLE: Oleoylethanolamide, an endogenous PPAR-. alpha. agonist, lowers body weight and hyperlipidemia in obese rats
AUTHOR(S): Fu, Jin; Oveisi, Fariba; Gaetani, Silvana; Lin, Edward; Piomelli, Daniele
CORPORATE SOURCE: Department of Psychiatry, University of California, Irvine, CA, USA
SOURCE: Neuropharmacology (2005), 48(8), 1147-1153
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The fatty-acid ethanolamide, oleoylethanolamide (OEA), is a naturally occurring lipid that regulates feeding and body weight, and serves as an endogenous agonist of peroxisome proliferator-activated receptor-alpha (PPAR-α), a ligand-activated transcription factor that regulates several aspects of lipid metabolism OEA reduces food intake in wild-type mice, but not in mice deficient in PPAR-α (PPAR-α-/-), an effect that is also observed with the PPAR-α agonists Wy-14643 and GW7647. By contrast, specific agonists of PPAR-δ/β (GW501516) or PPAR-γ (ciglitazone) have no such effect. In obese Zucker rats, which lack functional leptin receptors, OEA reduces food intake and lowers body-weight gain along with plasma lipid

levels. Similar effects are seen in diet-induced obese rats and mice. In the present study, we report that subchronic OEA treatment (5 mg kg-1, i.p., once daily for two weeks) in Zucker rats initiates transcription of PPAR-α and other PPAR-α target genes, including fatty-acid translocase (FAT/CD36), liver fatty-acid binding protein (L-FABP), and uncoupling protein-2 (UCP-2). Moreover, OEA decreases neutral lipid content in hepatocytes, as assessed by Oil red O staining, as well as serum cholesterol and triglyceride levels. The results suggest that OEA regulates lipid metabolism and that this effect may contribute to its anti-obesity properties.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 53 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:457004 CAPLUS
DOCUMENT NUMBER: 143:165756
TITLE: The potential use of PPARα agonists as immunosuppressive agents
AUTHOR(S): Cunard, Robyn
CORPORATE SOURCE: Research and Medicine Services, Division of Nephrology, UCSD and VASDHS 151, San Diego, CA, 92161, USA
SOURCE: Current Opinion in Investigational Drugs (Thomson Scientific) (2005), 6(5), 467-472
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Fibrates are peroxisome proliferator-activated receptor (PPAR)α ligands that have been used to treat hyperlipidemia and atherosclerosis for many years, and research has demonstrated that these agents have immunosuppressive effects. PPARα is expressed in multiple inflammatory cell types, and its ligands abrogate expression of inflammatory diseases. This review focuses on the use of fibrates in inflammatory disease models. It also describes proposed mechanisms of action of PPARα ligands and discusses the potential use of these medications as immunosuppressive agents.
REFERENCE COUNT: 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 54 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:405064 CAPLUS
DOCUMENT NUMBER: 142:447124
TITLE: Preparation of acylsulfonamide derivatives as acetyl-CoA carboxylase inhibitors, their pharmaceutical compositions, and their uses
INVENTOR(S): Ichinose, Hidehiro; Nihei, Yukio; Yamamoto, Takashi; Suzuki, Nobuyasu; Nakanishi, Eiji; Kondo, Nobuo
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2005119987	A	20050512	JP 2003-354530	20031015
PRIORITY APPLN. INFO.:			JP 2003-354530	20031015

OTHER SOURCE(S): MARPAT 142:447124
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agonist fibrates are used in dyslipidemia. Here their mechanism of action and the pre-clin. and clin. evidence for the use of these medications for the prevention and treatment of atherosclerotic disease is explored. In addition, the role of PPAR-δ and the possibilities for the role of dual-binding agonists are examined

REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 70 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:758039 CAPLUS
DOCUMENT NUMBER: 141:288479
TITLE: Peroxisome proliferator-activated receptor (PPAR)-α: A pharmacological target with a promising future
AUTHOR(S): van Raalte, Daniel H.; Li, Min; Pritchard, P. Haydn; Wasan, Kishor M.
CORPORATE SOURCE: Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Pharmaceutical Research (2004), 21(9), 1531-1538
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Springer Science+Business Media, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Peroxisome proliferator-activated receptor (PPAR)-α is a ligand-activated transcriptional factor that belongs to the family of nuclear receptors. PPAR-α regulates the expression of genes involved in fatty acid β-oxidation and is a major regulator of energy homeostasis. Fibrates are PPAR-α agonists and have been used to treat dyslipidemia for several decades because of their triglyceride (TG) lowering and high- d. lipoprotein cholesterol (HDL-C) elevating effects. More recent research has demonstrated anti-inflammatory and anti-thrombotic actions of PPAR-α agonists in the vessel wall as well. Thus, PPAR-α agonists decrease the progression of atherosclerosis by modulating metabolic risk factors and by their anti-inflammatory actions on the level of the vascular wall. This is confirmed by several clin. studies, in which fibrates have shown to reduce atherosclerotic plaque formation and the event rate of coronary heart disease (CHD), especially in patients suffering from metabolic syndrome (MS). MS is characterized by a group of metabolic risk factors that include obesity, raised blood pressure, dyslipidemia, insulin resistance or glucose intolerance, and a prothrombotic state, and its incidence in the Western world is rising to epidemic proportions. This review paper will focus on the functions of PPAR-α in fatty acid β-oxidation, lipid metabolism, and vascular inflammation. Furthermore, PPAR-α genetics, the clin. use of PPAR-α activators and their future perspective will be discussed.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 71 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:709257 CAPLUS
DOCUMENT NUMBER: 142:127183
TITLE: Effect of liver fatty acid binding protein (FABP) T94A missense mutation on plasma lipoprotein responsiveness to treatment with fenofibrate
AUTHOR(S): Brouillette, Charles; Bosse, Yohan; Perusse, Louis; Gaudet, Daniel; Vohl, Marie-Claude
CORPORATE SOURCE: Lipid Research Center, CHUL Research Center, Sainte-Foy, QC, G1V 4G2, Can.
SOURCE: Journal of Human Genetics (2004), 49(8), 424-432

CODEN: JHGEFR; ISSN: 1434-5161
PUBLISHER: Springer Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fenofibrate, a peroxisome proliferated activated receptor alpha (PPARα) agonist, has been shown to decrease plasma triglyceride (TG) and increase plasma high-d. lipoprotein (HDL) cholesterol levels despite a large interindividual variation in the response. Fenofibrate-activated PPARα binds to a DNA sequence element termed PPAR response element (PPRE) present in regulatory regions of target genes. A PPRE has been identified in the proximal 5' flanking region of the gene encoding the liver fatty acid binding protein (LFABP). LFABP is a small cytosolic protein of 14 kDa present in the liver and the intestine and is a member of the superfamily of the fatty acid binding proteins (FABPs). FABPs play a role in the solubilization of long-chain fatty acids (LCFAs) and their CoA-ester to various intracellular organelles. FABPs serves as intracellular acceptors of LCFAs, and they may also have an impact in ligand-dependent transactivation of PPARs in trafficking LCFAs to the nucleus. Since PPARs are known to regulate the transcription of many genes involved in lipid metabolism, the importance of LFABP in fatty acid uptake has to be considered. The aim of this study was to verify whether genetic variations in the LFABP gene may impact on plasma lipoprotein/lipid levels in the fasting state as well as on the response to a lipid-lowering therapy with fenofibrate on plasma lipids and obesity variables. We also wanted to verify whether the presence of the PPARα L162V mutation interacts with genetic variants in LFABP gene. To achieve this goal, we first determined the genomic structure of the human LFABP gene and then designed intronic primers to sequence the coding regions, all exon-intron splicing boundaries, and the promoter region of the gene in 24 patients showing divergent plasma lipoprotein/lipid response to fenofibrate. Sequence anal. revealed the presence of a T94A missense mutation in exon 3. Interspecies comparison revealed that threonine 94 is conserved among species. We subsequently screened another sample of 130 French Canadian subjects treated with fenofibrate for the presence of the LFABP T94A mutation. Carriers of the A94 allele were at increased risk to exhibit plasma TG levels above 2.00 mmol/l after treatment with fenofibrate [2.75 (1.03-7.34); OR 95% confidence interval (CI)]. In addition, carriers of the A94 allele were characterized by higher baseline plasma-free fatty acid levels (FFA) (p=0.01) and by a lower body mass index (BMI) (p=0.05) and waist circumference (p=0.005) than T94 homozygotes. Moreover, PPARα L162V and LFABP T94A showed to have a synergistic effect on BMI (p interaction = 0.03). These results suggest that the LFABP T94A missense mutation could influence obesity indexes as well as the risk to exhibit residual hypertriglyceridmia following a lipid-lowering therapy with fenofibrate.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 72 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:648355 CAPLUS
DOCUMENT NUMBER: 141:190602

TITLE: Preparation of N-cyclohexylaminocarbonyl benzenesulfonamides as agonists or partial agonists or antagonists of PPAR gamma

INVENTOR(S): Sahoo, Soumya P.; Koyama, Hiroo; Miller, Daniel J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004066963	A2	20040812	WO 2004-US689	20040113
WO 2004066963	A3	20041111		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
AU 2004207444	A1	20040812	AU 2004-207444	20040113
CA 2512879	A1	20040812	CA 2004-2512879	20040113
EP 1587535	A2	20051026	EP 2004-701735	20040113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2007504285	T	20070301	JP 2006-536529	20040113
US 2006111585	A1	20060525	US 2005-542287	20050715
PRIORITY APPLN. INFO.:			US 2003-440761P P	20030117
			WO 2004-US689 W	20040113

OTHER SOURCE(S): MARPAT 141:190602

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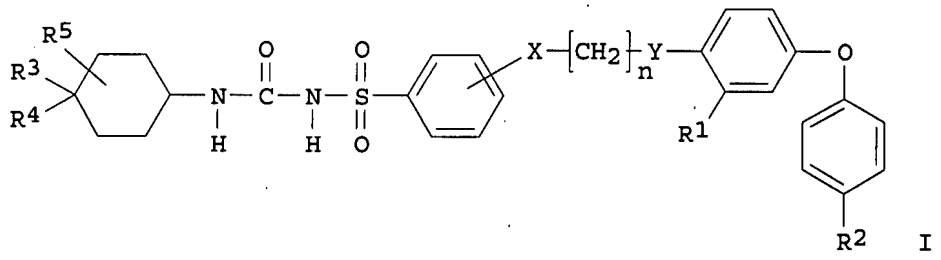

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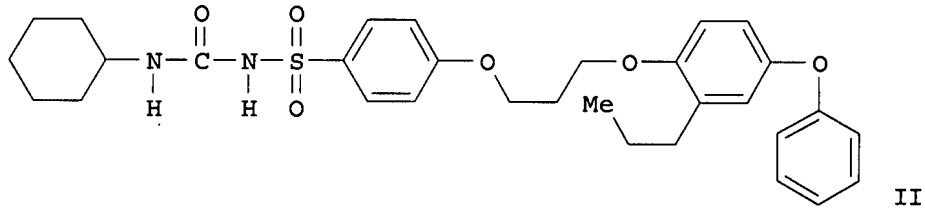


II

AB The title arylsulfonyl ureas [I; R1 = H, Cl, F, alkyl, haloalkyl; R2 = H, Cl, F, alkyl, alkoxy, etc.; R3-R5 = H, F, Cl, alkyl, etc.; X, Y = O, S, SO, SO2; n = 1-4] which are agonists or partial agonists or antagonists of PPAR gamma and are useful in the treatment and control of hyperglycemia that is symptomatic of type II diabetes, as well as dyslipidemia , hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, and obesity that are often associated with type 2 diabetes, were prepared Thus, reacting 1-(3-bromophenoxy)-4-phenoxy-2-propylbenzene with 4-hydroxybenzenesulfonamide in the presence of cesium carbonate in DMF followed by reaction of the resulting 4-[3-(4-phenoxy-2-propylphenoxy)propoxy]benzenesulfonamide with cyclohexyl isocyanate in the presence of potassium carbonate in acetone afforded II. The pharmaceutical composition comprising the compound I is claimed.

L5 ANSWER 73 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:524725 CAPLUS

DOCUMENT NUMBER: 141:64843

TITLE: The Peroxisome Proliferator-activated Receptor α (PPARα) Agonist

Ciprofibrate Inhibits Apolipoprotein B mRNA Editing in Low Density Lipoprotein Receptor-deficient Mice: effects on plasma lipoproteins and the development of atherosclerotic lesions

AUTHOR(S): Fu, Tao; Mukhopadhyay, Debnath; Davidson, Nicholas O.; Borensztajn, Jayme

CORPORATE SOURCE: Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, 60611, USA

SOURCE: Journal of Biological Chemistry (2004), 279(27), 28662-28669
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Low d. lipoprotein receptor (LDLR)-deficient mice fed a chow diet have a mild hypercholesterolemia caused by the abnormal accumulation in the plasma of apolipoprotein B (apoB)-100- and apoB-48-carrying intermediate d. lipoproteins (IDL) and low d. lipoproteins (LDL). Treatment of LDLR-deficient mice with ciprofibrate caused a marked decrease in plasma apoB-48-carrying IDL and LDL but at the same time caused a large accumulation of triglyceride-depleted apoB-100-carrying IDL and LDL, resulting in a significant increase in plasma cholesterol levels. These plasma lipoprotein changes were associated with an increase in the hepatic secretion of apoB-100-carrying very low d. lipoproteins (VLDL) and a decrease in the secretion of apoB-48-carrying VLDL, accompanied by a significant decrease in hepatic apoB mRNA editing. Hepatic apobec-1 complementation factor mRNA and protein abundance were significantly decreased, whereas apobec-1 mRNA and protein abundance remained unchanged. No changes in apoB mRNA editing occurred in the intestine of the treated animals. After 150 days of treatment with ciprofibrate, consistent with the increased plasma accumulation of apoB-100-carrying IDL and LDL, the LDLR-deficient mice displayed severe atherosclerotic lesions in the aorta. These findings demonstrate that ciprofibrate treatment decreases hepatic apoB mRNA editing and alters the pattern of hepatic lipoprotein secretion toward apoB-100-associated VLDL, changes that in turn lead to increased atherosclerosis.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 74 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:467861 CAPLUS

DOCUMENT NUMBER: 141:38443

TITLE: Preparation of phenyl substituted piperidines as PPAR agonists, in particular PPAR.alpha . agonists, and their pharmaceutical compositions and therapeutic use as hypolipemics, antidiabetics, etc.

INVENTOR(S): Bagley, Scott William; Brandt, Thomas Andrew; Dugger, Robert Wayne; Hada, William Andrew; Hayward, Cheryl Myers; Liu, Zhengyu

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: PCT Int. Appl., 196 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

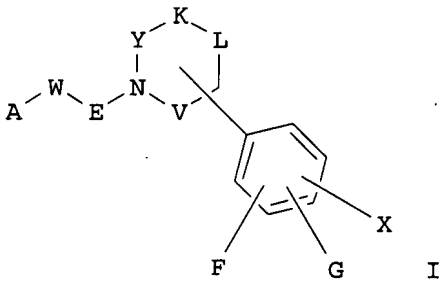
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004048334	A1	20040610	WO 2003-IB5235	20031114

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2507465	A1	20040610	CA 2003-2507465		20031114
AU 2003276596	A1	20040618	AU 2003-276596		20031114
EP 1567493	A1	20050831	EP 2003-811832		20031114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003016521	A	20051004	BR 2003-16521		20031114
CN 1717389	A	20060104	CN 2003-80104275		20031114
JP 2006509001	T	20060316	JP 2004-554809		20031114
US 2004157885	A1	20040812	US 2003-720942		20031124
US 7199243	B2	20070403			
NL 1024881	A1	20040527	NL 2003-1024881		20031126
IN 2005DN01615	A	20070119	IN 2005-DN1615		20050420
NO 2005002921	A	20050818	NO 2005-2921		20050615
PRIORITY APPLN. INFO.:			US 2002-429506P	P	20021126
			WO 2003-IB5235	W	20031114

OTHER SOURCE(S): MARPAT 141:38443
GI



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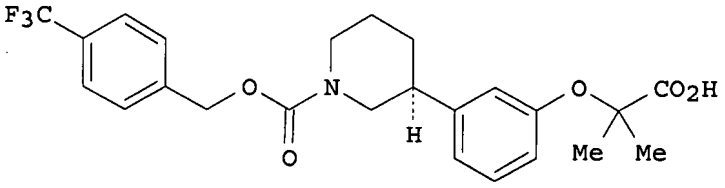

II

AB Title compds. I [wherein K = (CH2)m; L = (CH2)n; m, n = independently 1 or 2; V, Y = independently CH2, C(:O); F, G = independently H, halo, cycloalkyl, OH and derivs., alkylthio, (un)substituted alkyl; X = Z, B-CH2-Z and derivs.; B = O, S, SO, SO2, CH2, NH and derivs.; Z = CO2H and derivs., CONH2, tetrazolyl, etc.; E = CO, SO2, CH2; W = a bond, CO, NH and derivs., alkenyl, oxy, etc.; A = mono- or dialkylamino, alkanoylamino, alkoxy, (un)substituted (un)saturated 3-8 membered heterocycle or fused bicycle; with certain provisos; and their isomers, prodrugs and/or

pharmaceutically acceptable salts] were prepared as PPAR (peroxisome proliferator-activated receptor) agonists, and particularly as PPAR activators (no data). Disclosed are pharmaceutical compns. containing I, and the use of I to elevate certain plasma lipid levels, including high d. lipoprotein-cholesterol, and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides, and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases, in mammals, including humans. Further claimed uses include treatment of obesity, diabetes and related conditions, atherosclerosis, hypertension, inflammation, and thrombosis. For instance, II was prepared by adding (3S)-2-Methyl-2-[[3-(piperidin-3-yl)phenyl]oxy]propionic acid Me ester (preparation given) to a mixture of 4-(trifluoromethyl)benzyl alc. and CDI in toluene, followed by ester hydrolysis.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 75 OF 123 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:454436 CAPLUS

DOCUMENT NUMBER: 141:150792

TITLE: A novel selective peroxisome proliferator-activated receptor α agonist, 2-methyl-c-5-[4-[5-methyl-2-(4-methylphenyl)-4-oxazolyl]butyl]-1,3-dioxane-r-2-carboxylic acid (NS-220), potently decreases plasma triglyceride and glucose levels and modifies lipoprotein profiles in KK-Ay mice

AUTHOR(S): Kuwabara, Kenji; Murakami, Kohji; Todo, Makoto; Aoki, Tomiyoshi; Asaki, Tetsuo; Murai, Masatoshi; Yano, Junichi

CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2004), 309(3), 970-977
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB NS-220 was newly synthesized and demonstrated to be a novel potent peroxisome proliferator-activated receptor α (PPAR. alpha.) agonist with high subtype selectivity. In cell-based reporter gene assays, the EC50 values of NS-220 for human PPARα, PPARγ, and PPARδ were 1.9+10-8, 9.6+10-6, and >10-4 M, resp., and for mouse PPARα, PPARγ, and PPARδ were 5.5+10-8, 3.3+10-5, and >10-4 M, resp. In addition, [3H]NS-220 bound to the ligand-binding domain of human PPARα with a KD value of 1.85+10-7 M. Fenofibric acid and bezafibrate showed weak agonist activity for PPARα (EC50, 2-8+10-5 M), with poor subtype selectivity. NS-220 (0.1-3 mg/kg p.o.) decreased plasma triglyceride levels in ddY mice in a dose-dependent manner, but its hypolipidemic activity was abolished in PPARα-deficient mice. In KK-Ay mice, an animal model of type-2 diabetes, NS-220 (0.3-1 mg/kg p.o.; 4 days) and fenofibrate (100-300 mg/kg p.o.; 4 days) decreased plasma triglyceride and glucose levels in a dose-dependent manner. In a 2-wk repeated administration test, NS-220 (0.3-1 mg/kg p.o.) decreased plasma glucose levels markedly without increasing in plasma insulin levels. Furthermore, NS-220 increased high-d. lipoprotein levels and decreased triglyceride-rich lipoprotein levels. In conclusion, a newly synthesized dioxanecarboxylic acid derivative, NS-220, is a potent and highly selective PPARα agonist that ameliorates metabolic disorders in diabetic mice. These results strongly suggest that it will be a promising drug for the

treatment of hyperlipidemia or metabolic disorders in type-2 diabetes.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 14:28:06 ON 12 APR 2007)

FILE 'CAPLUS' ENTERED AT 14:28:26 ON 12 APR 2007

L1	478	S	PPAR ALPHA AGONIST?
L2	32441	S	DYSLIPIDEMIA OR HYPERCHOLESTEROLEMIA OR HYPERLIPIDEMIA OR HYP
L3	1308	S	HDL LEVELS OR LDL LEVELS
L4	33426	S	L2 OR L3
L5	123	S	L1 AND L4

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